UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

TXR# 0053566
Date: May 30, 2006

MORANDUM

SUBJECT: Fosthiazate [PC 129022] Request for a waiver of a DNT study for registration [MRID# 48784301]. Decision# 366357, DP Barcode: 328202.

FROM: David G Anderson, PhD
Re-registration Branch-2
Health Effects Division (7509P)

David G Anderson 5/30/06

To: Diana Locke, PhD
Risk Assessor
Re-registration Branch-2
Health Effects Division (7509P)

and Daniel Kenny and Rita Kumar,
Product Registration, RD (7505P)

THROUGH: Alan Nielsen, Branch Senior Scientist
Re-registration Branch-2
Health Effects Division (7509C)

Alan Nielsen 5/30/06

The sponsor has requested a waiver of a Developmental Study of Neurotoxicity [DNT] required as a condition for the re-registration of fosthiazate, technical. The request is denied.

A complete summary of the relevant toxicity data with fosthiazate was submitted to the Agency and is appreciated. However, none of the studies cited are able to show potential neurotoxic or behavioral effects resulting from *in utero* exposure. Possible neurotoxic developmental effects require special studies designed to detect these effects, which may depend on timing of exposure and developmental stage of the test species. Of the studies required, only the DNT study is designed to detect potential neurotoxic/behavioral effects resulting from exposure during stages of fetal development.

Although no residential exposure is anticipated, residues are expected on foods consumed by infants, children and potentially pregnant females. Residues can be expected on bananas, potatoes, tomatoes, peanuts and coffee as acknowledged.

Data submitted in support of the waiver.

1. Acute cholinesterase inhibition in rats
2. Acute neurotoxicity in rats
3. Acute delayed neurotoxicity in hens.
4. Four week range-finding study in rats

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5. Four week range-finding study in mice
6. 90-Day feeding study in rats
7. 90-Day feeding study in dogs
8. Review of adrenal pathology in the dog
9. Reevaluation of cholinesterase inhibition in the dog
10. 90-Day neurotoxicity study in the rat
11. Chronic/Oncogenicity study in the rat
12. Statistical analysis of cholinesterase values in the chronic rat study
13. Chronic Oral dog study
14. Developmental Study in the rat
15. Preliminary, range-finding and definitive developmental toxicity in the rabbit
16. Two-generation reproduction study in the rat
17. Comparative cholinesterase inhibition in dams and fetuses, adults, 11-day old pups and 21 day old pups from acute dosing and multiple-doses.

The relationship of neurotoxicity and cholinesterase inhibition appears to vary with the study. It is noted that the acute neurotoxicity study [MRID# 44269907] showed decreased grip strength and decreased plasma, erythrocyte and brain cholinesterase at the same LOAEL, while another acute cholinesterase study [MRID# 43534502] showed only plasma cholinesterase inhibition at similar dose levels to the former study. The subchronic neurotoxicity study shows decreased grip strength at higher doses than cholinesterase inhibition. However, until a developmental neurotoxicity study is conducted, it is unknown whether cholinesterase inhibition occurs at the lower doses than behavioral/neurotoxic effects from dosing during development. Potential effects during development are not adequately detected in standard developmental toxicity or reproduction studies. Most of the above studies may detect severe neurotoxicity and slight neurotoxicity in adults, however all of the above studies are inadequate and otherwise not designed to detect more subtle neurotoxic/behavioral effects resulting from exposure of the fetus during stages of development. A developmental neurotoxicity study is required.

In addition, fosthiazate is part of the cumulative assessment of the organophosphates and is needed for comparative purposes.

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R131989

Chemical: S-sec-Butyl O-ethyl (2-oxo-3-thiazolidinyl)phosphonothioate

PC Code:
129022
HED File Code: 11000 Chemistry Reviews
Memo Date: 5/30/2006
File ID: DPD328202
Accession #: 000-00-0108

HED Records Reference Center
8/24/2006